UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/556,145	08/21/2006	Richard Beliveau	0480-0165PUS1	5957

2292 7590 10/17/2007

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
GUSSOW, ANNE	
ART UNIT	**PAPER NUMBER**
1643	

NOTIFICATION DATE	DELIVERY MODE
10/17/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/556,145	BELIVEAU ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41 and 52-54* is/are pending in the application.

4a) Of the above claim(s) *1-9,11-13,16-31,33-35,39-41 and 52-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10,14,15,32 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/9/05, 5/3/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group III, claims 10-15 and 36-38, in the reply filed on August 22, 2007 is acknowledged.

2. Claims 1-9, 16-35, 39-41, and 52-54 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on August 22, 2007.

3. Claim 32 has been rejoined with Group III for examination.

4. This application contains claims directed to the following patentably distinct species: soluble p97 and an antibody directed to p97. The species are independent or distinct because they are antagonists with different structures and different functions. The species are independent or distinct because claims to the different species recite the mutually exclusive characteristics of such species. In addition, these species are not obvious variants of each other based on the current record.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, no claim is generic.

There is an examination and search burden for these patentably distinct species due to their mutually exclusive characteristics. The species require a different field of search (e.g., searching different classes/subclasses or electronic resources, or employing different search queries); and/or the prior art applicable to one species would not likely be applicable to another species; and/or the species are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

Applicant is advised that the reply to this requirement to be complete must include (i) an election of a species to be examined even though the requirement may be traversed (37 CFR 1.143) **and (ii) identification of the claims encompassing the elected species**, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

The election of the species may be made with or without traverse. To preserve a right to petition, the election must be made with traverse. If the reply does not distinctly and specifically point out supposed errors in the election of species requirement, the election shall be treated as an election without traverse. Traversal must be presented at the time of election in order to be considered timely. Failure to timely traverse the requirement will result in the loss of right to petition under 37 CFR 1.144. If claims are added after the election, applicant must indicate which of these claims are readable on the elected species.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record

showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the species unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other species.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141.

5. During a telephone conversation with Mark Newell on October 2, 2007 a provisional election was made to prosecute the species of soluble p97. Affirmation of this election must be made by applicant in replying to this Office action. Claims 11-13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

6. Claims 10, 14, 15, 32, and 36-38 are under examination.

Information Disclosure Statement

7. The information disclosure statements (IDS) submitted on November 9, 2005 and May 3, 2007 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Specification

8. The disclosure is objected to because of the following informalities: in the brief description of the figures, description of the specific sections (A, B, C, etc.) of figures 15, 16, 19, 23, 24, 26, and 27 is not included in the description of the figures.

Appropriate correction is required.

Claim Objections

9. Claim 10 is objected to because of the following informalities: the claim contains grammatical errors, for example the phrase "or an antibody an antibody" in line 3. Appropriate correction is required.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 36-38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating cancer caused by cells expressing melanotransferrin (p97), does not reasonably provide enablement for a method of treating just any cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or used the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method of treating cancer, comprising administering to an individual a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of one of melanotransferrin (p97), an enzymatically active fragment thereof, or an antibody recognizing specifically p97, or an antigen binding fragment thereof, in association with a pharmaceutically acceptable carrier, wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, intraarterially, transdermally or via a mucus membrane, wherein said cancer is selected from the group consisting of melanoma, prostate cancer, leukemia, hormone dependent cancer, breast cancer, colon cancer, lung cancer, skin cancer, ovarian cancer, pancreatic cancer, bone cancer, liver cancer, biliary cancer, urinary organ cancer (for example, bladder, testis), lymphoma, retinoblastoma, sarcoma, epidermal cancer, liver cancer, esophageal cancer, stomach cancer, cancer of the brain, cancer of the kidney, and metastasis thereof.

The specification discloses that exogenous p97 inhibits cell migration of HMEC-1 and SK-MEL28 cell lines (example V). The specification discloses soluble p97 inhibits angiogenesis in HMEC-1 and HUVEC cell lines. The specification does not disclose treatment of just any cancer with soluble p97.

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells

were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Further, both the treatment of cancer and or inhibition of angiogenesis in a host are quite unpredictable. For example, it was recently revealed that the drug Endostatin is unlikely to be the kind of across-the-board cancer cure that many had hoped for. Out of the 61 terminally ill patients tested, not one recovery had been seen (MSNBC News Services, "Mixed results on new cancer drug", November 9, 2000). Hence, it would not be predictable that a method drawn to inhibiting angiogenesis would be effective in a host in need thereof- such as a host suffering from cancer. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents

including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable that the method would function as

contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 10, 14, 32, 36-38 rejected under 35 U.S.C. 102(b) as being anticipated by Gabathuler, et al. (US PG PUB 20020119095, filed August 17, 2001).

The claims recite a method for treating cancer caused by cells expressing melanotransferrin (p97) at their surface, said method comprising the step of administering to a patient in need thereof exogenous soluble p97, said soluble p97 competing with the p97 expressed on the cell surface, activating plasminogen in solution instead of membrane-bound plasminogen, thus preventing cell migration, said antibody, or active fragment thereof binding p97 on the surface of the cell thus preventing activation of membrane-bound plasminogen, preventing cell migration, preventing cancer cells from spreading, wherein said cell is a tumor cell, wherein said cell is selected from the group consisting of human vascular or microvascular endothelial cells and human melanoma cells. A pharmaceutical composition for use in treating cancer comprising a therapeutically effective amount of one of melanotransferrin (p97), an enzymatically active fragment thereof, or an antibody

recognizing specifically p97, or an antigen binding fragment thereof, in association with a pharmaceutically acceptable carrier. A method of treating cancer, comprising administering to an individual a therapeutically effective amount of a pharmaceutical composition according to claim 32, wherein said administering is carried out orally, parenterally, subcutaneously, intravenously, intramuscularly, intraperitoneally, intraarterially, transdermally or via a mucus membrane, wherein said cancer is selected from the group consisting of melanoma, prostate cancer, leukemia, hormone dependent cancer, breast cancer, colon cancer, lung cancer, skin cancer, ovarian cancer, pancreatic cancer, bone cancer, liver cancer, biliary cancer, urinary organ cancer (for example, bladder, testis), lymphoma, retinoblastoma, sarcoma, epidermal cancer, liver cancer, esophageal cancer, stomach cancer, cancer of the brain, cancer of the kidney, and metastasis thereof.

Gabathuler, et al. teach a pharmaceutical composition comprising soluble p97 conjugated to a chemotherapeutic agent for treating brain tumors (page 9 paragraphs 79-83). Gabathuler, et al. teach p97 is a 97,000 Dalton protein also known as melanotransferrin that is a membrane associated protein and has been suggested as a melanoma specific cell marker (page 1 paragraph 3). Gabathuler, et al. teach intra-jugular injections of the pharmaceutical composition into mice (see example 11). Since the claims recite a composition comprising soluble p97, the p97 protein can be conjugated to other agents and all the limitations of the claims have been met.

Conclusion

14. No claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

October 9, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER